Remarks

Claim 1 has been amended to define dry microparticles having a size range of between 0.5 and ten microns comprising a drug to be delivered by inhalation, wherein the microparticles are formed of a material releasing drug at a pH of greater than 6.0, wherein the material is selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents. Support for the amendment is found, for example, on page 2, line 28.

Claim 21 was amended to correct a typographical error.

Claim 23 has been amended to define a method for delivery of microparticles to the pulmonary system comprising: administering to a patient in need of treatment an effective amount of microparticles which comprise a diketopiperazine and an active agent and which have a diameter between 0.5 microns and ten microns, in a pharmaceutically acceptable carrier for administration to the lungs, wherein the carrier is air, and wherein the active agent is released from the microparticle at a pH of greater than 6.0. Support for the amendment is found, for example, on page 17, line 18 to page 18, line 2 and page 3, lines 18-19.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 16-18 and 22 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention.

Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner alleges that there is no support in the specification for a material which releases a drug at pH of greater than 6, which includes mixed amino acids. Without making any admissions, and solely for the purpose of facilitating prosecution, claim 1 has been amended to define polymers of mixed amino acids. Support for the amendment is found, for example, on page 2, line 28. Claim 1, as amended, satisfies the written description requirement.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 23-26 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner alleges that essential elements are missing from claim 23, the omitted elements being *compressed* air and that the drug is released from the material at a pH greater than 6.0. Claim 23 has been amended to incorporate the release pH. With respect to the carrier, the applicants disclose that the microparticles can be delivered using a variety of methods including direct administration into the nasal passages, powder installation devices, dry powder inhalers, and catheters or tubes that reach into the pulmonary tract (page 22, lines 26-29. The use of compressed air is a preferred embodiment. The applicants do not disclose that compressed air is required. Therefore, claim 23 is definite.

The Examiner alleges that the term "agent" in claim 26 lacks antecedent basis. Claim 26 depends from claims 23. Claim 23 has been amended to define a microparticle comprising a diketopiperazine and an active agent. Claim 23, as amended, has proper antecedent basis.

Rejection Under 35 U.S.C. § 103

Claims 16 and 17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over European Patent No. EP 0 257 915 to Boyes *et al.* ("Boyes"). Claims 16 and 19-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,063,910 to Debenedetti *et al.* ("Debenedetti"). Claims 16 and 21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Japanese Patent Application No. JP 363020301 to Sugaya *et al.* ("Sugaya"). Claim 22 was rejected under 35 U.S.C. § 103(a) as being unpatentable over European Patent No. EP 0 257 915 to Boyles *et al.* ("Boyes") in view of U.S. Patent No. 4,866,051 to Hunt *et al.* ("Hunt"). Applicants respectfully traverse this rejection.

a. European Patent No. EP 0 257 915 to Boyes et al. ("Boyes")

Claim 16 defines dry microparticles having a size range of between 0.5 and ten microns comprising a drug to be delivered by inhalation, wherein the microparticles are formed of a material releasing drug at a pH of greater than 6.0, wherein the material is selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents.

Boyes describes microencapsulated drug particles typically in sizes in excess of 1 micron. The drug is encapsulated in a polymeric wall forming material and the resulting microcapsules

are exposed to a lipid-soluble surfactant or a surfactant is incorporated into the wall material of the microcapsule. Suitable polymeric materials include PGA, poly-d,l-lactic acid copolymers thereof, copolyoxylates, polycaprolactone, and poly(lactic acid-caprolactone). The microcapsules described in Boyes require two components: a polymeric wall forming material and a surfactant. In contrast, the claimed microparticles are formed from a material selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents. Boyes does not disclose or suggest microparticles formed from proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents. The polyhydroxyacids described in Boyes are not proteins, polymers of mixed amino acids, polysaccharides, lipids or surface active agents.

Claim 16 also requires that the material release the active agent at a pH of greater than 6.0. Claim 16 defines a subset of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents; namely those that release the drug at a pH of greater than 6.0. Boyes does not disclose or suggest dry microparticles wherein the microparticles are formed of a material releasing drug at a pH of greater than 6.0, wherein the material is selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents. Therefore, claims 16 and 17 are not obvious in view of Boyes.

b. U.S. Patent No. 6,063,910 to Debenedetti et al. ("Debenedetti")

Debenedetti describes passing a solution of a soluble material, preferably a protein, in a solvent through a continuum of supercritical antisolvent fluid and precipitating the material. The

resulting particulate material can be incorporated into a polymer matrix formed of polyhydroxy acids such as poly(L-lactic acid), poly(D,L-lactic acid), and polyglycolic acid. In contrast, the claimed microparticles are formed from a material selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents. Debenedetti does not disclose or suggest dry microparticles having a size range of between 0.5 and ten microns comprising a drug to be delivered by inhalation, wherein the material is selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents. Polyhydroxy acids are not proteins, polymers of mixed amino acids, polysaccharides, lipids, or surface active agents.

Claim 16 also requires that the material release the active agent at a pH of greater than 6.0. Claim 16 defines a subset of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents; namely those that release the drug at a pH of greater than 6.0. Debenedetti does not disclose or suggest dry microparticles wherein the microparticles are formed of a material releasing drug at a pH of greater than 6.0, wherein the material is selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents. Debenedetti does not disclose or suggest dry microparticle wherein the proteins are hydrophilic proteins or hydrophobic proteins (claims 19 and 20). Therefore, claims 16, 19, and 20 are not obvious in view of Debenedetti.

c. Japanese Patent Application No. JP 363020301 to Sugaya et al. ("Sugaya")

Sugaya describes microparticles prepared from chitosan with an average diameter of less than 10 m. The microparticles are prepared by dissolving chitosan in a 0.1% to 10% by weight aqueous solution of an acid, such as acetic acid or hydrochloric acid, to obtain an acidic aqueous solution of chitosan of a concentration of 0.05% to 20% by weight (abstract). The solution is spray-dried without a coagulant, a suspending agent, or the like (abstract). The microparticles can be used as a carrier material in the medical field (abstract).

Sugaya does not disclose or suggest including in the microparticles a drug to be delivered by inhalation. Further, Sugaya does not disclose or suggest that the release of a drug from the microparticles can be pH-mediated, let alone specify that the microparticles are designed to release a drug at a pH greater than 6.0. The Examiner alleges that Sugaya describes microparticles formed from the same material as the claimed compositions. The Examiner is incorrect. The claims do not define that the microparticle can be made from any protein, polymer of mixed amino acids, polysaccharide, lipid, or surface active agent; rather the claimed compositions defines those materials as those that release the drug at a pH greater than 6.0. Therefore, claims 16 and 21 are not obvious over Sugaya.

d. European Patent No. EP 0 257 915 to Boyles et al. ("Boyes") in view of U.S. Patent No. 4,866,051 to Hunt et al. ("Hunt")

As discussed above, Boyes does not disclose or suggest dry microparticles wherein the microparticles are formed of a material releasing drug at a pH of greater than 6.0, wherein the

material is selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents nor a cartridge for insertion into an inhaler comprising the same.

Hunt describes pharmaceutical compositions containing beclomethasone in the form of its micronized monohydrate (abstract). The compositions may be in the form of powder inhalation cartridges especially suitable for the treatment and/or prophylaxis of asthma (abstract). Hunt does not disclose dry microparticles having a size range of between 0.5 and ten microns comprising a drug to be delivered by inhalation, wherein the microparticles are formed of a material releasing drug at a pH of greater than 6.0, wherein the material is selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents.

In order to establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970). As discussed above, neither Boyes or Hunt discloses or suggests a cartridge for insertion into an inhaler comprising dry microparticles having a size range of between 0.5 and ten microns comprising a drug to be delivered by inhalation, wherein the microparticles are formed of a material releasing drug at a pH of greater than 6.0, wherein the material is selected from the group consisting of proteins, polymers of mixed amino acids, polysaccharides, lipids and surface active agents. Therefore, one of ordinary skill in the art would not be motivated to

combine Boyes and Hunt to arrive at the claimed cartridge. Accordingly, claim 22 is not obvious over Boyes in view of Hunt.

Allowance of claims 16-36, as amended, is respectfully solicited.

Respectfully submitted,

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